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Music: A Key for Unlocking Locked-in Syndrome and Improving the Quality of Life for Those with Neurodegenerative Diseases

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Abstract

Neurodegenerative diseases involve the gradual loss of neuronal functioning over time; such diseases include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease. The cause of these disorders is often idiopathic and treatment options are limited. Certain progressions of these diseases may lead to Locked-in-Syndrome, where an individual is aware of their environment but unable to communicate due to paralysis. The impact from these disorders often leads to further comorbidities and an overall lower quality of life. This paper addresses scientific literature on the effects of music on the brain and how music therapy can be used to help those with neurodegenerative disorders. Several studies show strong evidence to support music therapy as a means for improving cognitive, behavioral, and emotional functioning, as well as providing comfort care for individuals with AD and PD. Furthermore, a new type of eye tracking technology has even allowed individuals with complete paralysis to compose and deliver a musical performance through accessing brainwaves and eye movements. This technology has allowed individuals to deepen their engagement with their environment, also potentially improving their emotional well-being. Finally, this research illuminates the possibilities for music therapy to become a standard means for supporting individuals with neurodegenerative disorders.

Keywords: Music, brain, neurodegenerative, Alzheimer's disease, Parkinson's disease, Locked-in Syndrome

Music: A Key for Unlocking Locked-in-Syndrome and Improving the Quality of Life for Those with Neurodegenerative Diseases

Neurodegenerative diseases affect over 30 million individuals worldwide; they are particularly difficult to treat as they have unknown pathogeneses and limited treatment options (Sheikh, Safia, Haque, & Mir, 2012). In the US alone, approximately 5 million Americans live with AD, 1 million with PD, 30,000 with Huntington's disease, and 30,000 with ALS, and numbers are expected to rise ("The Challenge," 2001). Although comfort care and certain treatments may help, as of yet, no neurodegenerative disease has a cure.

Music has been shown to activate certain brain regions, influence neurotransmission, and increase brain plasticity, which becomes of importance when discussing treatment for abnormal brain functioning ("Musical Training," 2013). Furthermore, music therapies have shown promising results as a form of treatment for patients with AD and PD (Brotons & Marti, 2003; Pacchetti et al., 2000). Music has even been able to facilitate communication with the outer world for those with a form of severe paralysis called Locked-in Syndrome (Gaines, 2016). The neurological, behavioral, and emotional impacts from music therapy, as well as the benefits to both the affected individuals and their caregivers, are important considerations for evaluating the effectiveness of music therapy as a treatment option. If music therapy is significantly successful for patients with neurodegenerative disorders and patients with severe paralysis, there are further steps that should be taken to incorporate music therapy into a daily or weekly routine to better the lives of everyone affected by these disorders.

This literature review discusses an overview of the structure and functioning of the brain, connection between music and the brain, results of music therapy for those with neurodegenerative disorders, and a new technology that brings music therapy to those suffering from Locked-in Syndrome.

Literature Review

I. Neuroscience of the Brain

To understand how the brain engages with music and what brain irregularities appear in neurodegenerative disorders, it is important to understand the functioning of several major areas of the brain. The brain is divided into many sections and subsections, each with different functions, but all interconnected with the other regions (Swenson, 2006). One large section of the brain is called the cerebrum, which is divided into four major lobes: the frontal, parietal, occipital, and temporal (Figure 1). The outer layer of the cerebrum is called the cerebral cortex, which is about 2-3mm thick and is comprised of grey matter. The brain is also divided into two hemispheres, the left and right, which are connected through a structure made up of bundles of white matter fibers called the corpus callosum, which is responsible for coordinating and transmitting information between the two sides of the brain (Figure 2).

The function of the occipital lobe is interpretation of visual stimuli, while the temporal lobe is important for storing and processing short-term memories and auditory stimuli. The frontal lobe is involved with attention, planning, and integrating sensory and motor information, and is divided into two main subsections (MacDonald, Kreutz, & Mitchell, 2012). The prefrontal cortex, located most ventrally, has many functions, including involvement with working memory, sequencing of activities, abstract reasoning, dividing attention, impulse control, personality, and reactivity to surroundings and mood (Figure 5) (Swenson, 2006). The motor cortex, located most dorsally, is responsible for controlling body movements, and has somatotopic organization, meaning that very specific regions of this cortex correspond with specific nerves that control particular parts of the body (Figure 1).

The fourth cerebral lobe is the parietal lobe, which is involved with integrating sensory information, discriminating between objects, and language processing (“Parietal lobe,” 2000). Much like the frontal lobe, the parietal lobe can be divided into two important subsections. First, the association cortex is involved with integrating information from other parts of the brain. Second, the somatosensory cortex, which sits directly next to the motor cortex, exhibits somatotopic organization like the motor cortex, but is involved with processing sensory stimuli (Swenson, 2006). Directly below cerebrum is the cerebellum, which is responsible for maintaining balance, coordination and timing of muscle movements, and motor learning (Knierim, 1997).

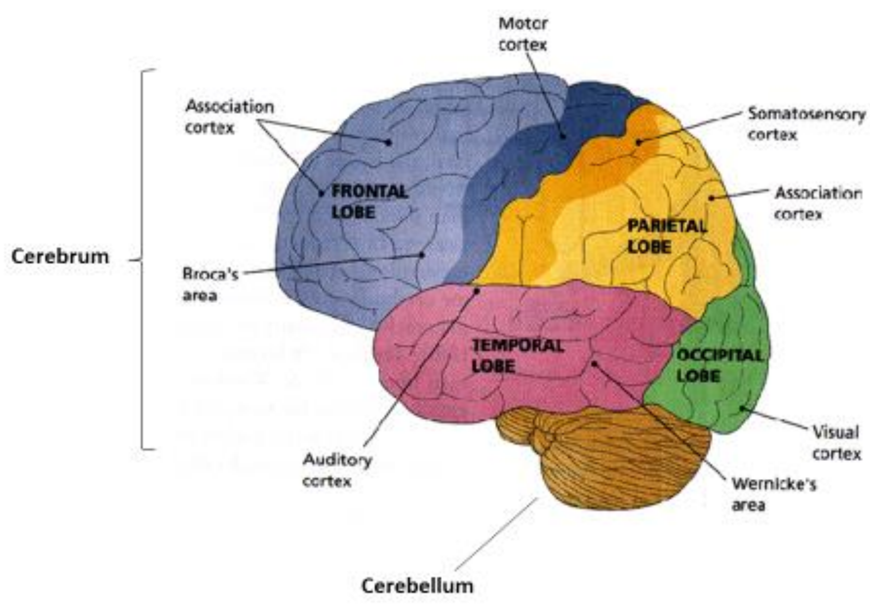

Figure 1: Lateral view of the cerebral lobes and the cerebellum (Missy, 2008).

Directly beneath the cerebral cortex lies the inner brain structures, including the limbic system (Swenson, 2006). This system is involved with emotion and memory, and is comprised of structures including the thalamus, hypothalamus, hippocampus, amygdala, cingulate gyrus, and basal ganglia. The thalamus is involved in relaying motor and sensory information to the cortex, the hypothalamus maintains homeostasis, and the hippocampus helps with short-term memory formation. The cingulate gyrus and amygdala are involved in the processing of complex emotions, with the amygdala being particularly associated with fear and anxiety.

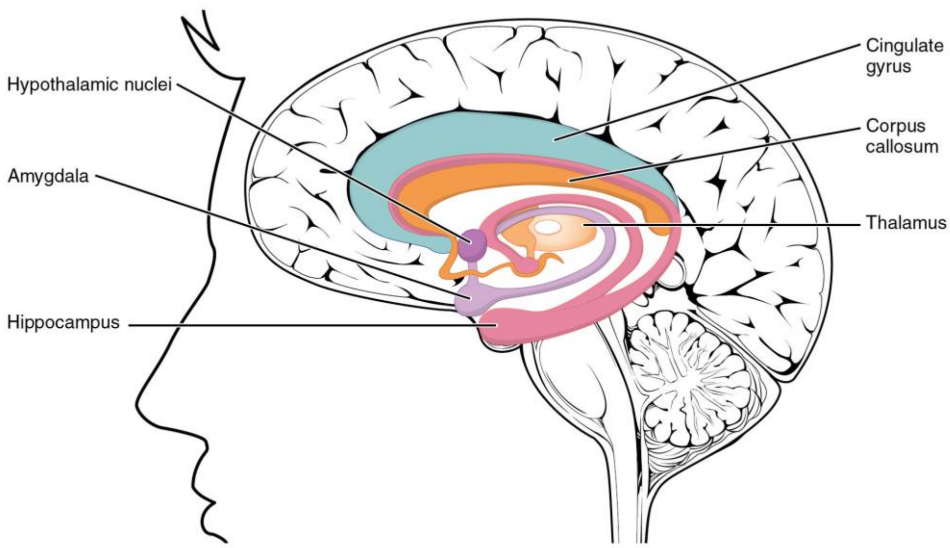

Figure 2: A longitudinal cross-section of the brain illustrating the inner brain structures including the corpus callosum and the limbic system ("Anatomy", 2013).

The basal ganglia system is comprised of several different structures including the nucleus accumbens (ventral striatum), caudate nucleus, putamen, subthalamic nucleus, and substantia nigra (Figure 3) (Knierim, 1997). Along with being important for emotion and memory, the basal ganglia system is important for the control of movement (Leisman, Melillo, &

Carrick, 2013). Improper functioning of the activity in the basal ganglia system is directly related to Parkinson's disease.

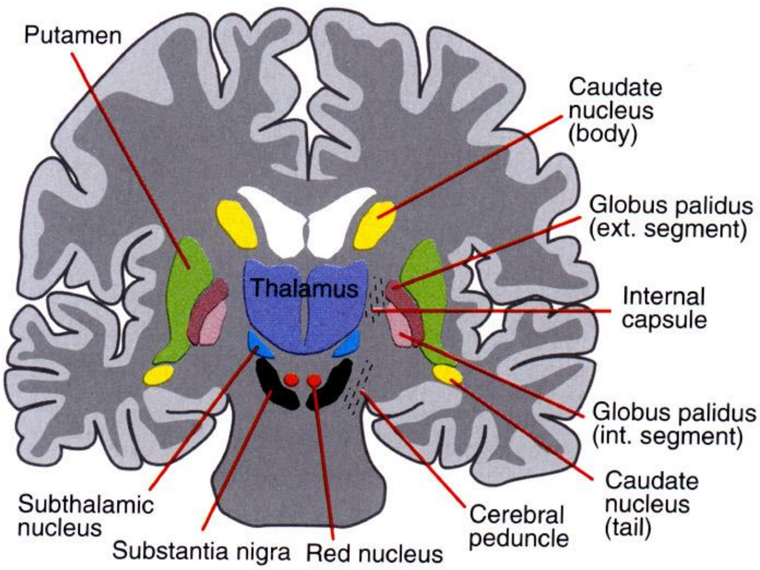

Figure 3: A coronal cross-section of the brain illustrating the structures of the basal ganglia (nucleus accumbens not shown) (Leisman, Melillo, & Carrick, 2013).

The functional units of the brain are composed of trillions of modified cells called neurons that are organized into functional clusters (Lodish et al., 2000). The signaling between these neurons is essential for proper brain functioning, and degeneration or misfiring of these neurons can be the cause of certain disorders. Information in the brain is transmitted via electrical and chemical signaling from one neuron to the next. First, a signal from another neuron or the outer environment is received by receptors on the dendrites of a presynaptic neuron (Figure 4). This signal is then transduced into an electrical signal, which travels down the axon to the end of the neuron where it will trigger the release of chemicals called neurotransmitters into the synapse. The synapse, or synaptic cleft, is the small gap between two neurons. From the synapse, the neurotransmitters are then taken up by receptors on a postsynaptic neuron, from where the signal can be further propagated from one neuron to the next until it reaches the proper brain region needed for processing. Some important neurotransmitters include glutamate, acetylcholine, dopamine, norepinephrine, epinephrine, and serotonin. There is an insulating fatty layer that surrounds the axon of the neuron, which is called the myelin sheath. This layer helps to facilitate the speed of transmission of a neuronal signal. Glial cells, such as Schwann's cells and satellite cells, also facilitate neuronal signaling by removing dead neurons, making myelin, and providing physical support and nutrients to the neuron (Gleason, 2014).

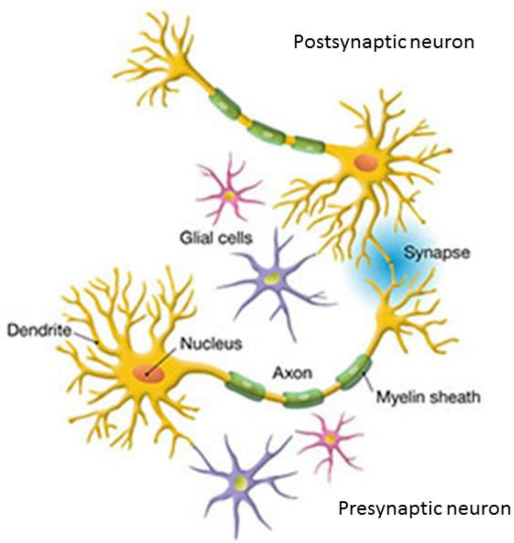

Figure 4: Neuron structure and synaptic communication between neurons (Gleason, 2014).

The brain is also highly dynamic. Neuronal pathways may change and new neuronal pathways can form between brain cells; this ability of the brain to adapt over time is known as brain plasticity (Green & Bavelier, 2008). When a particular neuronal pathway is practiced repeatedly, over time, synaptic connections will strengthen, a phenomenon called long-term potentiation (Purves et al., 2001).

II. The Brain and Music

The experience of listening to, playing, or interacting with music engages many parts of the brain that deal with visual and auditory sensory pathways, motor control, memory, and emotion (MacDonald et al., 2012). Hence, many brain regions are activated when engaging with music, including cerebral regions such as the frontal, occipital, and temporal lobes, and somatosensory and motor cortices (Figures 5 & 6). One study presented at a Society for Neuroscience conference by Yunxin Wang illustrated the effects of music on the cerebral cortex (*Musical Training*, 2013). Wang compared the brain structures of children who had musical training to those who had not, and found that that the cerebral cortex was much larger in participants who had previous musical training, particularly for those who had started their musical training before age seven. Additionally, the cerebellum is activated when engaging with music, particularly when movement must occur at a certain time, such as during the playing of rhythms (Figures 5 & 6) (MacDonald et al., 2012).

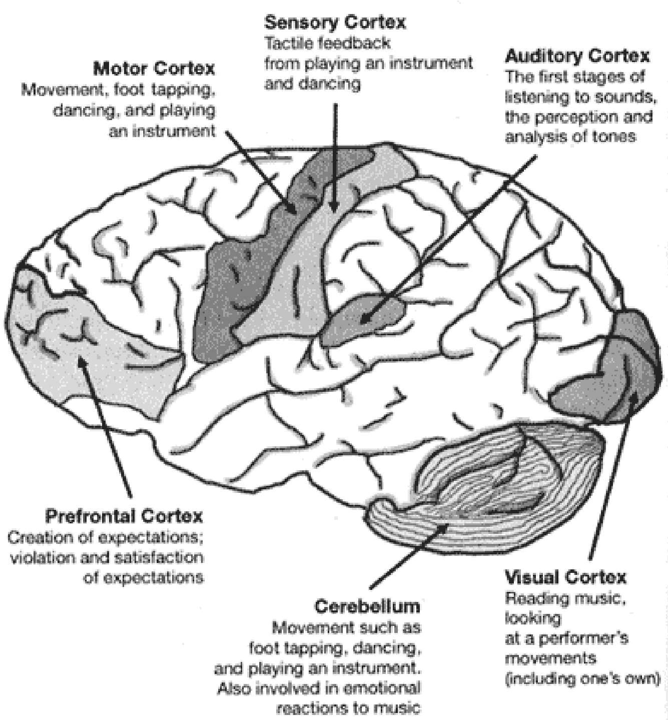

Figure 5: Cortical regions that are activated when engaging with music (Levitin, 2006).

Often, music will also activate the limbic system, (particularly the amygdala, nucleus accumbens, and hippocampus) which is important for evoking memories and an emotional response to music (Figure 6) (MacDonald et al., 2012; Levitin, 2006). This widespread activation of the limbic system may explain how music can allow a breakthrough of seemingly normal emotions in individuals who cannot usually express emotions. Oliver Sacks, in his book *Musicophelia* (2008), tells several anecdotes of patients he had seen who suffered from an inability to express normal emotions. These included patients with a severe brain trauma, post-encephalitic brain damage, schizophrenia, and autism. When subjected to a form of music they enjoyed, all momentarily transformed from having a flat affect into individuals who sang, danced, and expressed emotions.

Additionally, music, emotion, and memory are strongly correlated with one another. A study by Buchanan (2007) demonstrated the link between emotions and memory by showing that strong emotions could act as a memory enhancer due to higher arousal levels during these strong emotions. The link between emotion and memory is also shown through cases where emotional regions of the brain are damaged and subsequent memory consolidation does not occur properly (Buchanan & Adolphs, 2004). Furthermore, Eschrich, Munte, & Altenmuller (2008) examined the correlation between emotion, arousal, and music, and showed that music that evokes strong emotions has a particular impact in facilitating memory formation and retrieval. Listening to music causes increased blood flow to brain areas and changes in brain activation, thereby evoking responses to emotion and memory (Jäncke, 2008) and giving music a key role in emotional arousal and memory enhancement.

In addition to activation of the limbic system, music may enhance brain regions involved in communication between the brain hemispheres. In a longitudinal study by Hyde et al., (2009) a relationship was found between the size of the corpus callosum and musical training. This study compared children who were given 15 months of keyboard training to those who had no training, and results showed that the corpus callosum was larger and more developed in the musical training group. This study showed a correlation between musical training, structural brain changes, and behavioral improvements, as measured by finger dexterity. Hyde demonstrates the positive effects of music on brain plasticity and long-term potentiation, as the brains of those with musical training exhibited structural changes, as well as developed strengthened pathways that promoted improved motor behavior. Although this study evaluated healthy children, researchers noted that the results could have important implications for helping children with developmental disorders as well for adults with neurological diseases.

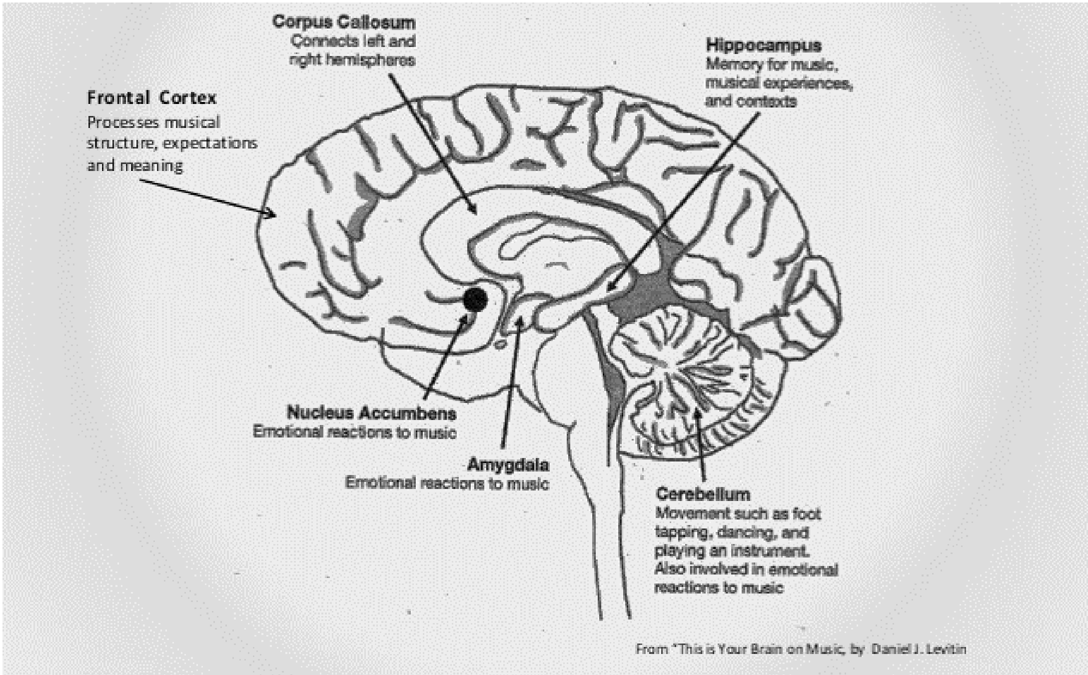

Figure 6: Internal brain structures that are activated when engaging with music (Levitin, 2006).

Additionally, a review of the Society for Neuroscience Conference highlighted studies that show further evidence that the brain can develop in response to repeated engagement with music (*Musical Training*, 2013). One such study by Julie Roy (2013) compared the sensory capabilities of people who had played a musical instrument for a year or more to those who had not. Results demonstrated that the musicians had a greater capability of integrating sensory information. Another study by Ana Pinho (2013) assessed the brain activity of classical and jazz musicians and showed that musical improvisation leads to more connectivity of brain tissue, and less dependence on working memory.

Furthermore, several studies have tried to pinpoint the specific brain changes that occur with long-term musical training. Although the exact details are still unknown, researchers have found that microstructural brain changes can occur, including increased number of synapses, development of more glial cells, increased density of capillaries, generation of new brain cells, and increased density of grey and white brain matter (Black et al., 1990; Hyde et al., 2009; MacDonald et al., 2012).

Along with the activation of certain brain areas, music also stimulates the release of certain neurotransmitters, particularly dopamine (MacDonald et al., 2012). Dopamine is closely associated with reward-motivated behavior and movement, which are important for the process of learning and practicing music. Increased dopaminergic activity provides a strong link between learning and memory (Wise, 2004), and may be a factor influencing increased brain plasticity in musicians.

Since much evidence strongly supports the connection between music and the brain, this poses questions for how music could be used as therapy to help those with brain abnormalities, such as for those affected by neurodegenerative disorders. Furthermore, with knowledge of the pathology of neurodegenerative disorders, might it be possible to elucidate a mechanism for how music therapy may be effective for these individuals?

III. Neurodegenerative Diseases and Music Therapy

Neurodegenerative diseases are characterized by the gradual loss of neuronal functioning over time (Sheikh et al., 2012). Because the nervous system is central to brain functioning and body movement, the gradual degradation of neurons in such diseases can lead to types of dementia, mood changes, and paralysis. Some neurodegenerative diseases include Alzheimer’s, Parkinson’s, and Huntington’s diseases as well as amyotrophic lateral sclerosis (ALS). Many other dementias, motor neuron, viral-related, and prion diseases are also categorized as neurodegenerative diseases (“Disease”, 2017). Because more research is available for more common diseases, the focus of this paper will be on Alzheimer’s and Parkinson’s diseases.

Alzheimer’s Disease

Alzheimer’s disease (AD) is characterized by a gradual loss of memory, and is the most common cause of dementia in the elderly (Agamanolis, 2016). As AD progresses, different types of memory are gradually lost starting with short-term memory followed by episodic memory, semantic memory, and then procedural memory (Mastin, 2010). Episodic refers to memory of autobiographical events, semantic to memory of common facts about the world, and procedural to memory of how to perform tasks. Individuals with AD may experience learning difficulties, loss of language functioning, inaccurate perception of space, and a decrease in overall cognitive functioning (Agamanolis, 2016). Patients with AD may also have deficits with social functioning and comorbid depression. Furthermore, the suprachiasmatic nucleus, which is responsible for circadian rhythm, naturally changes morphologically as we age, but this change is enhanced in patients suffering from AD (Wittig, Kwa, Eikelenboon, Mirmiran, &Swaab, 1990). Individuals with AD often have disruptions in circadian rhythm, including abnormal rest-activity periods, increased awakenings at night, and more nocturnal activity, which are correlated with the severity of the dementia.

In AD, several neurodegenerative changes occur in many brain regions including the temporal lobe, parietal lobe, frontal cortex, cingulate gyrus, hippocampus, cerebral cortex (Wenk, 2003). These changes include gross brain atrophy, neuronal degeneration, and presence of amyloid plaques and neurofibrillary tangles and are all thought to contribute to the presentation of Alzheimer’s dementia (Figure 7) (Agamanolis, 2016). Loss of neuronal functioning is seen particularly in cholinergic neurons (Wenk, 2003), which are involved with the transport of the neurotransmitter acetylcholine. Amyloid plaques, or senile plaques, are made up of beta amyloid, which is an insoluble fragment of a large protein that accumulates over time because enzymes are unable to degrade it properly (Agamanolis, 2016). Neurofibrillary tangles (NFTs) are hyper-phosphorylated tau protein fragments that aggregate together and form helical deposits. The build-up of amyloid plaques and NFTs in AD impairs cellular functioning and neuronal synaptic communication.

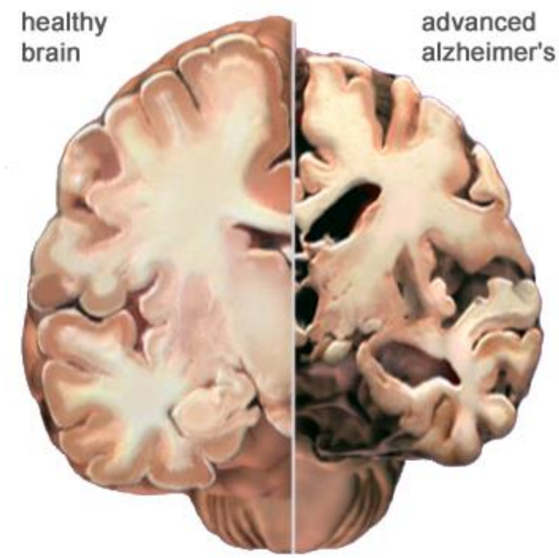

Figure 7: Comparison of brain structure showing abnormal brain atrophy in AD (“More brain changes”, 2011).

Although there are suggested lifestyle changes to help prevent or delay onset of AD, there are currently no effective treatments to halt the progression of AD (Mastin, 2010). The most commonly used medications are cholinesterase inhibitors, which include donepezil, galantamine, and rivastigmine (Kaduszkiewicz, Zimmerman, Beck-Bornholdt, & van den Bussche, 2005). These inhibitors work by preventing the degradation of acetylcholine, thereby keeping more acetylcholine in the synaptic cleft, available for neuronal activities related to learning and memory (Becker & Giacobini, 1988). Memantine is another drug available for AD that works by inhibiting an NMDA receptor, thereby regulating the activity of glutamate, a neurotransmitter necessary for learning and memory (Tariot et al., 2004). Although these medications may help Alzheimer's symptoms, they have many side effects and still provide no cure.

Alzheimer's Disease and Music Therapy

Music therapy will not cure AD, but it has been shown to help improve behavioral, emotional, and cognitive functioning for those with AD. For example, several types of music therapies are used depending upon the stage of AD, the desired outcome of the therapy, and what the individual responds to (Clair & Tomaino 2016). In the early stages of AD, music therapy may involve playing an instrument the individual had played previously in their life, while music therapy for later stages may include listening to a folk song from their early childhood. Different types of music therapy may also be tailored to changing a certain behavior, or evoking an emotion connected with a certain tune. Because of the variety in types of music therapy and the spectrum of how people are affected by AD, treatment is very individualized.

Several studies have demonstrated that music therapy is an effective method for altering behaviors in individuals with AD. Brotons and Pickett-Cooper (1996) conducted a study that tested agitation behaviors before, during, and after exposure to music therapy, and found that the subjects with AD were less agitated during and after music therapy than before therapy. Additionally, they found music therapy was effective in decreasing agitation behaviors like pacing and crying, which were ranked as highly stressful for caregivers. Conclusions from this study suggest that music therapy is beneficial for reducing caregiver stress and may lower rates of burnout for staff caring for patients with AD. Another study by Svansdottir and Snaedal

(2006) showed that music sessions were effective in reducing both aggressiveness and anxiety in those with AD. They also suggested that participation in music sessions could give more meaning to the lives of patients with AD through being involved in meaningful musical activities. Leger and Baker (2006) claim that although there is strong evidence supporting short-term reductions in agitation, no significant evidence shows a long-term reduction in agitation behaviors. However, they also note that music therapy is cheap, easy, and safe and can provide a vital intervention strategy for caregivers and those with AD.

Different types of music may also be used to help with specific behavioral outcomes. Stimulatory music with an upbeat rhythm can help promote movement and greater arousal, which may be used if a patient needs to engage in an activity that requires more movement such as eating or bathing (Clair & Tomaino 2016). Other types of soothing, sedative music such as a ballad or lullaby may help relax the individual or help with sleep.

A study by Adarsh Kumar et al. (1999) showed that music may have implications for helping with common circadian rhythm issues (such as those mentioned previously) in patients with AD. This research showed that music therapy intervention for 30 to 40 minutes in the morning, five days a week for a month, showed a significant increase in levels of serum melatonin, norepinephrine, and epinephrine. These levels also lasted for six weeks after music therapy was stopped. Increased levels of epinephrine and norepinephrine will affect the levels of melatonin, a hormone involved with the control of circadian rhythm and sleep cycles, which may help individuals with AD return to more normal sleep behaviors.

Music therapy may also be advantageous to the patient by activating the limbic system and evoking an emotional response. Music that triggers an emotional response for the listener has been found to be a more effective therapy option (Clair & Tomaino 2016). Therefore, because of different memories and music preferences, the type of music used is very individualized to the listener. For example, the music playlist on an iPod may be chosen by a family member to evoke a particular emotional response or memory for the individual with AD and allow for greater positive effects from the music ("Music on the Brain", 2016).

Songs that trigger a close association to a particular memory can have significant effects on both emotion and cognitive functioning. Generally, individuals respond strongest to tunes from music in their young adult years, ages 18-25 (Clair & Tomaino 2016). In the later stages of dementia, however, the most influential songs may be ones from early childhood, such as folk tunes, that evoke memories formed very early in life. As an individual reacts emotionally to music, they also exhibit a change in behavioral and cognitive functioning as they become more animated and may begin to recall earlier memories ("Music on the Brain", 2016).

Several cases have been documented that show this effect on emotions, cognitive functioning, and behavior in individuals with AD, but one paramount example is the story of Henry. As a patient with advanced AD, but who had a love of music, Henry would often be found slumped over, with a severely diminished ability to interact with the outer world. But when given an iPod and headphones that played music that he recognized from his past, his face immediately became more animated, he could engage in more motor activities, interact with those around him, and even began to sing. The stimulatory effects of this music lasted for several hours after the music was stopped and, furthermore, Henry could answer questions about his past in better detail. Henry's story can be found at <https://m.youtube.com/watch?v=fyZQf0p73QM>, which is a video clip from a short documentary called Alive Inside: A Story of Music and Memory, which highlights stories of individuals with AD who have been helped by music therapy (Rossato-Bennett, 2014).

The precise mechanistic reasons for the effectiveness of music therapy for those with AD are still unknown, but several factors may be involved. Firstly, engagement with music requires little high-level cognitive processing, therefore even when cognitive functioning is gradually lost in AD, one is still able to engage with music (Clair & Tomaino 2016). Secondly, as seen with the study by Kumar (1999), music stimulates the synthesis of certain neurotransmitters, which play a part in regulating mood and sleep behaviors. Adjusting behaviors, such as regulating sleep cycles, can have positive impacts that treat different symptoms and eventually have greater therapeutic downstream effects.

Thirdly, it may be that the strong connection between music, emotion, and memory, as discussed previously, is an important part of the therapy's effectiveness. As music activates the limbic system, it activates the emotion and memory centers of the brain, which can help enhance memory (Buchanan, 2007), and which can have large therapeutic effects for those with AD. Furthermore, engagement with music involves more than just listening to music, so if an individual actively engages with music through singing, dancing, or communicating with other individuals, activation of so many areas of the brain could be a reason for the effectiveness of music therapy (Sauer, 2014).

Even if the reasons for why music therapy is effective is not yet elucidated, sufficient evidence shows that music can improve mood and serve as a form comfort care to improve the patient's well-being ("Music on the Brain", 2016; Brotons & Marti, 2003). Furthermore, an improved mood in an individual with AD not only benefits that individual, but also provides happiness and excitement for their caregivers. Seeing a loved one with improved ability to remember and interact with their environment can be reassuring and comforting for family members and caregivers alike.

In many aspects of medicine, medications are available to treat physiological conditions, but there has been little progress in ways for treating the soul. In diseases that have no cure, such as AD, it becomes increasingly important to pay attention to providing a good quality of life and providing comfort wherever possible. Sufficient evidence has shown that music therapy is an effective treatment strategy that can be a strong component of comfort care without negative side-effects, and should therefore be included as a more standard means for therapy for individuals with AD.

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease (de Lau & Breteler, 2006). According to the Parkinson's Disease Foundation, the cardinal signs of PD include a resting tremor, bradykinesia (slow movement), rigidity of the limbs, and instability while standing upright ("Symptoms", 2017). Additional symptoms may be present such as freezing of gait, unwanted acceleration of movement (particularly with gait and speech), and a mask-like expression where a person loses animation in the face. Furthermore, non-motor symptoms may also exist and generally precede a PD diagnosis, which may include mood disorders, sleep disturbances, constipation and bladder issues, and sexual problems.

The cause of the disease is still unknown; some studies suggest that mitochondrial dysfunction, oxidative stress, and protein mishandling may play a role in the development of PD, but the specific mechanisms are still largely unknown (de Lau & Breteler, 2006). Currently, scientists have observed that PD is inherited as an autosomal dominant or autosomal recessive trait, which suggests that a single gene may be the cause of some forms of PD (Lucking & Brice, 2000). However, specific genetic factors are still unknown but are thought to play a role in predisposing a person to developing PD, while environmental factors such as sleep and eating habits may trigger further development of PD (Wirdefeldt, Adami, Cole, Trichopoulos, & Mandel, 2011). In some cases, certain factors, such as having REM sleep behavior disorder (RBD), are correlated with an increased risk for PD while other cases of sporadic PD, for example, may have no genetic link (Wirdefeldt et al., 2011). According to a recent study on the correlation between RBD and PD, 30% of patients tested with RBD developed PD within three years, with the percent rising to 66% of patients with RBD developing PD within 8 years (Postuma, Gangon, Bertrand, Marchand, & Montplaisir, 2015).

A hallmark sign of PD is the presence of Lewy bodies in the brain, which are aggregates of protein that contain alpha-synuclein (Lucking & Brice, 2000). Through a still unknown mechanism, Lewy bodies aggregate and somehow disrupt neuronal functioning and can cause cell death. Parkinson’s disease is characterized by the degeneration of neuronal pathways, specifically of dopaminergic neurons in the substantia nigra, located in the basal ganglia system of the brain (Figure 8) (Leisman, Melillo, & Carrick, 2013).

Although there are supportive treatments for PD, there is still no cure (de Lau & Breteler, 2006). Treatment with dopamine has been shown to be effective for helping to stabilize Parkinsonian symptoms (Hammond, Bergman, & Brown, 2007). Levodopa is a standard drug for PD that has been effective for improving symptoms, which works by being converted into dopamine as it enters the brain. After five to ten years however, the drug is associated with motor complications in 80% of patients. Other treatment options are available such as surgical intervention involving deep-brain stimulation, but complications may exist and treatment does not cure the life-long disease. Despite treatment with drugs or surgery however, many symptoms of Parkinson's still persist, leaving treatment options limited to comfort care (Dreu, van der Wilk, Poppe, Kwakkel, & vanWegen, 2011).

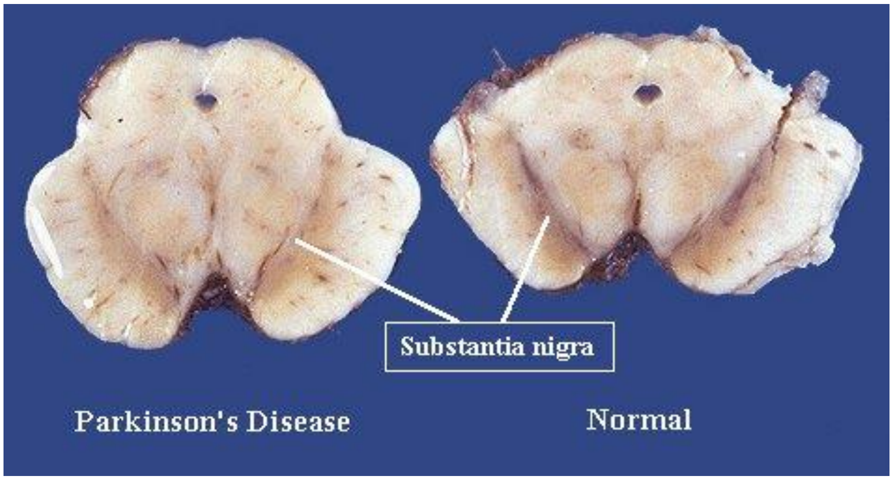

Figure 8: Comparison of midbrain section showing loss of substantia nigra cells in Parkinson's Disease (Crimando, 2013).

Parkinson's Disease and Music Therapy

Fortunately, more and more research is being done in the use of music therapy as a form of treatment for Parkinson's disease. Auditory stimulation paired with movement exercises is becoming an increasingly common therapeutic strategy (Dreu et al., 2011). A study by Nieuwboer et al. (2007) that used a cueing therapy home program for patients with PD showed that cueing therapy significantly helped improve gait in those that received treatment. The cueing therapy program involved pairing an auditory, visual, or somatosensory cue with the rhythm of an individual's gait. They found that this cueing training helped a wide range of patients with different aspects of their gait. It helped to increase walking speed and step amplitude, while reducing step frequency and severity of freezing. Because freezing is very difficult to treat, researchers noted this was a particularly important benefit of music therapy.

An important aspect of this cueing with music therapy is that the music provides a stimulus to make the individual develop a desire to move, activating other motor pathways that then cause the individual to move on command (Dobson, 2017). One patient named Rosalie, described in Oliver Sack's book *Musicophelia* (2007), illustrates this phenomenon quite well. Sack's describes Rosalie as a patient with Parkinson's who remained motionless for most of the day, but when she sat down to play piano however, her whole body moved and her expression changed, becoming quite animated. Sacks observed that Rosalie could also become animated by merely imagining playing piano, however, she could not bring herself to this point on her own. Instead, it was essential that she had a cue, which soon became the words "Opus 49", which immediately enabled Rosalie to imagine playing and become animated again. This phenomenon has been documented in other patients with cues such as "climb me" to help the individual get out of bed.

Further studies have been done that show that rhythmic auditory stimulation (RAS) can help gait abnormalities such as freezing, shuffling steps, and start hesitation in individuals with PD (Ashoori, Eagleman, & Jankovic, 2015). RAS may include music and dance therapies that have a steady tempo and are targeted towards helping an individual with PD move more naturally. One example of music therapy significantly helping an individual was featured on ABCTV Catalyst where music helped a man named John transform his walk from a freezing of gait where his feet shuffled along the floor quickly to one where he was able to step and dance to the beat of the music ("Music on the Brain", 2016).

Like music therapy treatments for Alzheimer's disease, music therapy for patients with PD are unique to the individual and depend on the purpose of the treatment (Dobson, 2017). For example, some types of music may help increase the urge to move, while others may help facilitate relaxation and sleep. The effectiveness of a type of music therapy however depends on music preference, memories, and the emotions triggered by a piece of music.

Overall, music therapy has been shown to help with motor, affective, and behavioral functioning in those with PD (Pacchetti et al., 2000). Music therapy may be used to help organize muscle movements in many areas of the body in individuals with Parkinson's (Dobson, 2017). For example, for those where speech is impaired due to lack of motor control of facial muscles, singing may be part of a therapy to improve control of these muscles.

A meta-analysis study by Dreu et al. (2011) further demonstrates that music not only influences the body's physiology, but also helps to improve mood and emotions, provide a distraction and a form of comfort care, improve patient compliance with therapies, and facilitate group and social interactions. Music therapy can be effective as a stand-alone therapy for those with PD, but can also be used as a strategy to enhance other therapies, especially well when partnered with dance. Furthermore, music therapy may help treat comorbidities associated with Parkinson's such as depression, anxiety, and feelings of social isolation (Dobson, 2017). Joining a music therapy group, can provide a way to connect to others, promote physical activity, and increase emotional health.

Although similar in many ways to therapy for AD, the effectiveness of music therapy for individuals with PD may have more to do with the idea of increased dopamine in response to music. A group of researchers in Japan has done several studies on the mechanisms that cause increased dopamine synthesis in response to music. One study in 1989 by Sutoo and Akiyama found conclusive evidence supporting a model proposing that increased calcium leads to increased dopamine synthesis. The findings of this study led Sutoo and Akiyama to further research the effects of music on calcium and dopamine levels in the brain (2004). Researchers exposed rats to music for 15-120 minutes and then measured serum calcium levels and brain dopamine levels. They found that all groups that had exposure to music had significantly higher calcium levels than the non-music control group. When examining dopamine with a brain-mapping analyzer and immunohistochemical fluorescence, they found a significant increase in dopamine in specific brain regions, namely the neostriatum in the basal ganglia system. The conclusions from this work indicated that both calcium and dopamine levels increase during exposure to music, which suggests further implications for treatment for diseases where dopamine is deficient, such as Parkinson's disease.

IV. Locked-in Syndrome

Since music therapy has so many benefits those with neurodegenerative disorders, the next pressing question is whether music therapy can be used elsewhere, particularly to benefit others with severe paralysis. Although there are many forms of paralysis, I will focus on a form called Locked-in Syndrome (LIS). Individuals with LIS often have normal cognitive functioning, sensation, and emotional capabilities, but are unable to communicate due to near complete paralysis (Maiese, 2016).

There are three classification categories for LIS: classic, incomplete, and total (Smith & Delargy, 2005). In the classic and incomplete categories, an individual may have quadriplegia and anarthria (inability to speak remembered words) with preserved consciousness. A patient in the classic category would have vertical eye movements, while a patient in the incomplete category would have remnants of movement other than vertical eye movement. The third category is characterized by complete immobility and inability to communicate, yet still with full consciousness.

Individuals with LIS may exhibit difficulties due to their paralysis, such as inability to chew, swallow and speak due to ataxia (paralysis) of the lower face and neck behavioral abnormalities, respiratory insufficiency, and excessive salivation (Maiese, 2016). Individuals may also present with cerebral palsy, diplopia, spasticity, tetraparesis, tetraplegia (Bruno & Laureys, 2012). Affected individuals have normal sleep-wake cycles and their emotional capabilities are still fully functioning, although some individuals may exhibit pathologic crying or laughing. Even in classic or incomplete LIS, communication is exceedingly difficult, and individuals may become hopeless as they feel “trapped” in their own bodies (Holley, 2015). Despite EEG readings that show the patient is conscious (Smith & Delargy, 2005) patients may be mistaken as unconscious and may be treated as such, with little respect to their emotions (Maiese, 2016). With the frustrations that arise from paralysis combined with a prognosis of a life expectancy of 1-20 years with little chance of recovery, (Bruno & Laureys, 2012) LIS can be very frustrating and emotionally taxing for both the individual and their caregivers.

Although recovery is rare, one case of a man named Martin Pistorius, who woke up from LIS, has helped illuminate the feelings of an individual with LIS. A quote from Martin describing his life while paralyzed states, "It's like a cold, sinister frustrating and frightening feeling, which seems to throttle every cell in your body…It's was like you're a ghost witnessing life unfold in front of you and nobody knows you are there” (Holley, 2015).

LIS may appear suddenly, as the result of some trauma, or may be a result of a late stage of progression of a degenerative disease (Smith & Delargy, 2005). Most often, LIS is caused by damage to the ventral pons of the brain, most commonly by an infarction, hemorrhage, or trauma. Other causes for LIS include damage to the ventral pons from an infection, tumor, or demyelination commonly from multiple sclerosis.

There is no mainstream treatment other than symptomatic and supportive care including physical therapy to prevent muscle contractions, medication to prevent respiratory infections and ulcers, nutritional support, and comfort care (Maiese, 2016). The use of eye movements and blinking can lead the way for communication to the outside world if an individual works closely with a speech therapists to establish a blinking code for communication.

V. A Key for Locked-in Syndrome

Due to the nature of LIS, treatment options are limited, but music therapy can have particular importance as a form of treatment for individuals with LIS to provide a key for unlocking their minds from the prisons of their bodies. Unlike individuals with AD and PD, patients with LIS are not easily able to interact physically with music because they are limited by their physical constraints. Therefore, we must look to new technologies, which show promising opportunities for individuals with LIS to engage with music and benefit from the emotional joy it brings.

Several new technologies that tap into the brain-computer interface have been developed and are slowly increasing in popularity (Bruno & Laureys, 2012). One particular technology has allowed individuals with LIS to be able to compose music in a group setting and hear their composition played back to them by live musicians (Gaines, 2016). This technology taps into the brainwaves and eye movements of individuals with LIS to send signals to a computer that selects a particular excerpt of music. This information of music selection is then sent to a screen where several live musicians can then play the selected piece of music for the listening audience. This technology has allowed individuals with LIS to not only interact with music, but also to interact with others through composing music together. A video showing this technology can be found at <https://www.ucdavis.edu/news/study-finds-brain-hub-links-music-memory-and-emotion>.

This eye-tracking technology has opened doors for individuals with LIS by allowing them to re-engage with their environments in a way that previously seemed impossible. This form of music therapy benefits the emotional and mental health of individuals with LIS because if they can communicate with, and even create, music they may find a better sense of purpose and not feel like a burden on their families. Furthermore, communication with technology can help caregivers to interact with the individual, reassuring them that a fully conscious person lies beneath the paralyzed body. Facilitating communication between family, caregivers, and individuals with LIS through music therapy can reduce feelings of loneliness, increase sense of belonging, and overall enhance quality of life.

Conclusions and Future Study

Examination of the interactions between music and the brain have demonstrated the close relationship between the two and the benefits that music can have on the brain. Knowledge of this relationship can provide insight into the mechanisms for why music therapy can be effective in treating individuals with neurodegenerative diseases. Because sufficient evidence has shown support for the effectiveness of music therapy as a treatment for AD and PD, this poses questions for future research into music therapy for individuals with other neurodegenerative diseases, such as Huntington’s disease and amyotrophic lateral sclerosis (ALS), or Lou Gehrig’s disease.

In all neurodegenerative disorders, neuronal function is decreased, causing a diminishment in mental and physical functioning. The similarities between these diseases provides evidence for how music can benefit many individuals with different disorders, and provides reasoning for how music therapy could be used as a treatment for all types of neurodegenerative disorders. Furthermore, all neurodegenerative diseases have a large psychological toll with limited treatment options and no cure. As seen with AD and PD, music therapy can provide a large component for comfort care, which could likely have the same positive outcome for those with other neurodegenerative diseases.

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